REMARKS

Claims 2-4, 6-9, 14-16, 18-20, 25-27, 30-32, 36, 39, and 42-44 are cancelled without prejudice or disclaimer. Claims 1, 5, 10, 17, 21-24, 28, 29, 33, 35, 40, 46, and 48 are currently amended. Some of the amended claims were withdrawn by the Examiner. Claims 49-52 are new. Support can be found, e.g., in the original claims or claims previously pending.

Traversal of Requirement for Species Election

Applicant has amended the generic claims and respectfully submits that the generic claims are patentable over the prior art. As the Examiner stated on page 3:

> If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims. In particular, it does not matter if a dependent claims itself contains a further invention. Equally, no problem arises in the case of a genus/species situation where the genus claim avoids the prior art.

The generic claims have been amended and are not anticipated by Haldimann. According to the passage quoted above from the most recent Action by the Examiner, each dependent claim should also be examined. Thus, all withdrawn claims should now be examined. Applicant does not accede to the Examiner's characterization of PCT Rule 13.1, and reserves the right to petition for proper examination pursuant to the rule as there is no basis for limiting examination to particular dependent claims. Applicant respectfully submits that all pending claims should be examined.

Indefiniteness

The Examiner alleges that the recitation of "heterologous metabolite" is indefinite. The Applicant disagrees, but has amended the claims to expedite prosecution.

The Examiner alleges that claim 9 is indefinite for recitation of "other enzymes." Claim 10 has been amended and no longer recites this phrase. The first and second enzymes refer to different enzymes for the biosynthesis of an isoprenoid.

Written Description Rejection

The Examiner has rejected claims 1-5, 7, 9, 10, 12, 13, 16-21, 24-27, 29, 30, 33-36, and 40-45 for lack of written description. Although the claims have been amended to expedite prosecution, Applicant does not accede to the Examiner's written description rejection and reserves the right to argue the rejection in subsequent or other applications.

The scope of the claims has been narrowed substantially. The claims now recite a host cell that is an *E. coli* host cell. The promoter is a promoter that is bound by ntrC, e.g., one that includes an ntrC binding site. For example, Sevenich (IDS Item BK) and references cited therein describe exemplary sequences bound by ntrC. It is axiomatic that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, 'Written Description' Requirement," Federal Register, Vol. 66, No. 4, 1099, 1106 (2001). Thus, Applicant's recitation of a promoter bound by ntrC is sufficiently described in view of the prior art's recognition of the sequences of ntrC binding sites.

Enablement Rejection

The Examiner has rejected claims 1-5, 7, 9, 10, 12, 13, 16-21, 24-27, 29, 30, 33-36, and 40-45 for lack of enablement. The claims are amended. Some claims (for example, claim 10) are limited to the subject matter that the Examiner has deemed enabled. Moreover, claims relating to promoters controlled by ntrC are also enabled in view of the teachings of Sevenich, *supra*.

Although the claims have been amended to expedite prosecution, Applicant does not accede to the Examiner's enablement rejection and reserves the right to argue the rejection in subsequent or other applications. Since the claims have been amended as discussed above, Examiner's concerns about enablement should be obviated. Moreover, the Examiner's attention is drawn to the high level of skill in the art of transcription factors and prokaryotic genetics and the teachings of the specification.

§ 103 Rejections

The Examiner has rejected claims 1-5, 7, 9, 16-20, 24-26, 30, 31, 34, 36, and 42-45 as obvious over WO96/08567 ("Liao") or Kajiwara in view of Bock, McCleary (AK), McCleary (AP), Haldiman, and Feng. The Examiner alleges, in part, on page 18 as follows:

> [I]t would have been obvious . . . to replace the lac promoters in the constructs of Kajiwara et al. with a promoter which is induced by high acetyl phosphate levels. As McCleary et al. teach that acetyl-phosphate level correlate with the amount of glycolytic intermediates produced, it would have been obvious to one of ordinary skill in the art to link the idi gene to the acetyl-phosphate regulated promoters taught by Haldiman et al. or Feng et al. and express these constructs in E. coli cells which lack the cognate histidine kinases such that the response regulators which activate transcription from these promoters are activated by acetyl phosphate.

Applicant respectfully traverses since there is no motivation to combine the cited references. Prior to this invention, acetate was generally considered detrimental to growth of bacterial cells and production of recombinant proteins. For example, Aristidou (IDS Item BD) states at column 1, page 475:

> Acetate is a lipophilic agent that is harmful to cell growth. Moreover, experimental results in our laboratory agree well with common observation that recombinant gene expression is greatly reduced for acetate accumulation above 15-25 mM.

Bauer (IDS Item BE) is to similar effect. See, for example, column 1, page 1296:

> Organic acids accumulate in the culture medium during aerobic growth of *Escherichia coli* on glucose. The most abundant organic acid is often acetic, and its concentrations can build up to levels that are inhibitory to growth. In a previous study, we showed that intracellular accumulation of interleukin-2 (IL-2) . . . was inversely correlated with cell density and acetate accumulation in fermentor cultures. These observations provided circumstantial evidence that acetate was at least partially responsible for the cessation of product accumulation during expression of heterologous genes in *E. coli* . . . .

Given these detrimental effects of acetate on recombinant protein production, one would not have been motivated to use a promoter that is regulated by acetyl phosphate to produce a heterologous polypeptide that catalyzes a reaction in a metabolic pathway which produces an isoprenoid. Applicant is unaware of any teaching in WO96/08567, Kajiwara, Bock, McCleary

(AK), McCleary (AP), Haldiman, or Feng which suggests that the undesirable conditions in which acetate accumulates would be suitable for producing a metabolite such as an isoprenoid.

Second, there is no expectation of success. The cited references do not provide a reasonable expectation that, under conditions in which acetate accumulates, that recombinantly expressed enzymes would have sufficient precursor substrates to produce an isoprenoid in *E. coli*.

Double Patenting Rejection

The claims were also provisionally rejected for double patenting in view of claims 36-40 of 09/626,612, now U.S. 6,706,516. In view of the provisional nature of the rejection and the amendment of the claims in the instant application, Applicant respectfully requests that the rejection be re-considered and/or held in abeyance. Should the rejection be maintained, Applicant may submit a terminal disclaimer.

Applicant does not concede any positions of the Examiner that are not expressly addressed above, nor does the Applicant concede that there are not other good reasons for patentability of the presented claims or other claims.

Enclosed is a $475 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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